NATIONAL GUIDELINE CLEARINGHOUSE™ (NGC)
GUIDELINE SYNTHESIS

LIPID SCREENING IN THE PRIMARY PREVENTION OF CORONARY HEART DISEASE AND ATHEROSCLEROTIC CARDIOVASCULAR DISEASE IN ADULTS

Guidelines

1. National Heart, Lung, and Blood Institute (U.S.) (NHLBI). (1)Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). (2)Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Bethesda (MD): U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung and Blood Institute; 2001. Various p. [1274 references]; Circulation 2004 Jul 13;110(2):227-39. [45 references]
2. United States Preventive Services Task Force (USPSTF). Screening for lipid disorders in adults: recommendations and rationale. Am J Prev Med 2001 Apr;20(3 Suppl):73-6. [12 references]
3. University of Michigan Health Systems (UMHS). Screening and management of lipids. Ann Arbor (MI): University of Michigan; 2003 April. 15 p. [7 references]
4. Veterans Health Administration, Department of Defense (VHA/DoD). VHA/DoD clinical practice guideline for the management of dyslipidemia in primary care. Washington (DC): Veterans Health Administration, Department of Defense; 2001 Dec. Various p. [115 references]

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INTRODUCTION:

A direct comparison of NHLBI, USPSTF, UMHS, and VHA/DoD recommendations for lipid screening in adults are provided in the tables below. These guidelines differ somewhat in scope. The NHLBI, UMHS, and VHA/DoD guidelines address both cholesterol testing and clinical management of high cholesterol, including secondary prevention; the USPSTF guideline addresses lipid screening only. This synthesis focuses on screening for lipid disorders for primary prevention of coronary heart disease (CHD) and atherosclerotic cardiovascular disease (ASCVD) in adults. Guidelines that include recommendations for clinical management of dyslipidemia will be covered in a separate synthesis.

Table 1 gives a broad overview of the four guidelines. Table 2 details the recommendations for lipid screening and risk factor assessment for adults. Benefits and harms associated with screening are listed in Table 3. The supporting evidence is classified and identified with the major recommendations for each guideline, and the definitions of each rating scheme are included in Table 4. Table 4 also includes references supporting specific recommendations for VHA/DoD, when applicable. Following the content comparison tables and discussion, the areas of agreement and differences among the guidelines are identified.

In formulating their recommendations, VHA/DoD drew heavily from NHLBI's Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATPIII]) and from the 1996 USPSTF recommendations for lipid screening contained in the Guide to Clinical Preventive Services, 2nd edition. UMHS also refers frequently to the NCEP report (ATP III) in its guideline on screening and management of lipids. USPSTF completed their guideline before the release of the ATPIII recommendations, and thus refer to ATP II (the 1993 NCEP report).

Notably, since the publication of ATP III, 5 major clinical trials of statin therapy with clinical end points have been published. These trials addressed issues that were not examined in previous clinical trials of cholesterol-lowering therapy. In 2004 the NHLBI issued an addendum to their guideline that reviews the results of these recent trials and assesses their implications for cholesterol management. Proposed modifications to the NHLBI guideline recommendations have been included in this synthesis.

Listed below are common abbreviations used within the tables and discussions:

- ATPII and ATPIII, Adult Treatment Panel II and Adult Treatment Panel III

- ASCVD, atherosclerotic cardiovascular disease
- BP, blood pressure
- CAD, coronary artery disease
- CHD, coronary heart disease
- CVD, cardiovascular disease
- DM, diabetes mellitus
- FH, familial hypercholesterolemia
- HDL, high-density lipoprotein
- LDL, low-density lipoprotein
- NCEP, National Cholesterol Education Program
- NHLBI, National Heart, Lung, and Blood Institute
- RCT, randomized controlled trial
- TLC, therapeutic lifestyle changes
- TC, total cholesterol
- UMHS, University of Michigan Health Systems
- USPSTF, United States Preventive Services Task Force
- VHA/DoD, Veterans Health Administration, Department of Defense

TABLE 1: SCOPE	
	Objective
NHLBI (2001 & 2004)	• To examine the available evidence on coronary heart disease (CHD) and high blood cholesterol, especially the evidence that has emerged since the second report of the Expert Panel was published in 1993 (Second report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [Adult Treatment Panel II]. Bethesda [MD]: U.S. Department of Health and Human Services, National Institutes of Health, National Heart, Lung and Blood Institute; 1993 Sep. 180 p.) • To update, where appropriate, the existing recommendations for management of high blood cholesterol in adults 2004 Addendum • To review the results of five recent clinical trials and assess their implications for cholesterol management • To translate the scientific evidence into guidance that helps professionals and the public take appropriate action to reduce the risk for coronary heart disease and cardiovascular disease
USPSTF (2001)	• To present recommendations for screening for lipid disorders • To update the 1995 recommendations contained in the Guide to Clinical Preventive Services, second edition

UMHS (2003)	• To present recommendations for primary and secondary prevention of coronary heart disease and stroke by outlining strategies for lipid screening, identifying patients who would benefit from treatment, and recommending appropriate treatment regimens
VHA/DoD (2001)	• To incorporate information from several existing national recommendations into a format which would facilitate clinical decision-making • To improve local management of patients with dyslipidemia and thereby improve patient outcomes
Target Population	
NHLBI (2001 & 2004)	• All adults aged 20 years or older
USPSTF (2001)	• All men aged 35 years and older and women aged 45 years and older • Men aged 20 to 35 years and women aged 30 to 45 years with risk factors for CHD
UMHS (2003)	• Adults 20-75 years of age without familial or severe dyslipidemias
VHA/DoD (2001)	• Adults (>17 years) eligible for care in the U.S. Department of Defense (DoD) or Veterans Health Administration (VHA) health care delivery system
Intended Users	
NHLBI (2001 & 2004)	• Advanced Practice Nurses • Dietitians • Nurses • Patients • Pharmacists • Physician Assistants • Physicians • Public Health Departments
USPSTF (2001)	• Advanced Practice Nurses • Allied Health Personnel

	• Health Care Providers • Nurses • Physician Assistants • Physicians
UMHS (2003)	• Advanced Practice Nurses • Dietitians • Nurses • Physician Assistants • Physicians
VHA/DoD (2001)	• Advanced Practice Nurses • Allied Health Personnel • Dietitians • Nurses • Physician Assistants • Physicians
Screening and Risk Assessment Interventions Considered	
NHLBI (2001 & 2004)	• Fasting lipoprotein profiles (TC, LDL-cholesterol, HDL-cholesterol, and triglyceride) • Identification of major risk factors as well as life-habit and emerging risk factors • Estimation of 10-year CHD risk with Framingham scoring
USPSTF (2001)	• Fasting or nonfasting TC and HDL-cholesterol Note: measurement of LDL-cholesterol and triglycerides are considered in patients with elevated screening results
UMHS (2003)	• Fasting or nonfasting TC and HDL-cholesterol • Fasting lipid profile (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides) • Assessment of CHD risk factors • Assessment of secondary causes of hyperlipidemia
VHA/DoD (2001)	• Patient history and assessment of risk factors • Measurement of TC and HDL or TC, HDL, triglycerides (TG), and LDL-cholesterol • Fasting lipid profile, including LDL • Consideration of possible secondary causes of elevated LDL-cholesterol using measurement of serum thyroid-stimulating hormone (TSH), blood urea nitrogen (BUN)/creatinine, and

	dipstick urinalysis • Consideration of possible secondary causes of hypertriglyceridemia by screening for alcohol use, reviewing dietary habits, and evaluating possible drug side effects (e.g., progestins, estrogens, androgens, anabolic steroids, corticosteroids, cyclosporine, and retinoids)

TABLE 2: COMPARISON OF RECOMMENDATIONS FOR LIPID SCREENING IN THE PRIMARY PREVENTION OF CORONARY HEART DISEASE AND ATHEROSCLEROTIC CARDIOVASCULAR DISEASE	
Who should be screened?	
NHLBI (2001 & 2004)	• Screening should begin at age 20, at the first appropriate opportunity presented by a visit to a physician (case finding), in both men and women.
USPSTF (2001)	• The USPSTF strongly recommends that clinicians routinely screen men aged 35 years and older and women aged 45 years and older for lipid disorders (A recommendation). An age to stop screening is not established. Screening may be appropriate in older persons who have never been screened, but repeated screening is less important in older persons because lipid levels are less likely to increase after age 65. • The USPSTF recommends that clinicians routinely screen younger adults (men aged 20-35 years and women aged 20-45 years) for lipid disorders if they have other risk factors for coronary heart disease, such as diabetes, a family history of cardiovascular disease before age 50 years in male relatives or age 60 years in female relatives, a family history suggestive of familial hyperlipidemia, multiple coronary heart disease risk factors (e.g., tobacco use, hypertension). (B recommendation) • The USPSTF makes no recommendation for or against routine screening for lipid disorders in younger adults (men aged 20-35 years or women ages 20-45 years) in the absence of known risk factors for coronary heart disease. (C recommendation)
UMHS (2003)	• Screening is recommended for men age 35-65, and women age 45-65. • Screening is optional for men age 20-34 and women age 20-44. • Screening should be considered in both men and women, ages 65-75 based on life expectancy.

VHA/DoD (2001)	• Targeted lipid screening of males aged 35 to 75 years and females aged 45 to 75 years is recommended in the primary prevention setting, based on the results of randomized controlled trials (RCTs) of lipid interventions. For every given age, the atherosclerotic cardiovascular disease (ASCVD) risk for a female is the same as that for a male 10 years her junior. • The recommendation for screening up to age 65 is based on strong clinical and epidemiologic evidence. The recent AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study) trial results (Downs et al., 1998) suggest that treating patients age 65-73 is beneficial. Epidemiologic evidence suggests benefit in ages 65 to 75. The association of cholesterol and mortality weakens in elderly patients, and screening is not recommended for primary prevention after age 75. • The risk of ASCVD is so low in males younger than 35 years and females younger than 45 years that screening cannot be recommended unless there is an unusual family history of coronary events occurring prior to age 45.
What type of screening test should be used?	
NHLBI (2001 & 2004)	• A fasting lipoprotein profile is recommended, including major blood lipid fractions (i.e., total cholesterol, LDL-cholesterol, HDL -cholesterol, and triglycerides). • If the testing opportunity is nonfasting, only the values for TC and HDL will be usable. In such a case, if total cholesterol is $\geq$200 mg/dL or HDL is <40 mg/dL, a follow-up lipoprotein profile is needed for appropriate management based on LDL.
USPSTF (2001)	• A fasting or nonfasting TC and HDL-cholesterol test is recommended. (B recommendation) Abnormal results should be confirmed by a repeated sample on a separate occasion, and the average of both results used for risk assessment. • There is insufficient evidence to recommend for or against measurement of triglycerides as part of routine screening for lipid disorders. (I recommendation)
UMHS (2003)	• Fasting or non-fasting TC and HDL-cholesterol is recommended (Level of Evidence: D). • A full lipid profile is also an appropriate option. Patients with abnormal non-fasting screening lipids (TC >200 mg/dL or HDL-cholesterol <40 mg/dL) should go on to have a fasting lipid panel

VHA/DoD (2001)	• Lipid levels may be obtained in a fasting or nonfasting state. • TC levels and HDL-cholesterol can be measured in the nonfasting patient. • TG concentrations, however, are affected by recent food intake and will affect the calculation of LDL-cholesterol by the Friedewald equation: LDL-cholesterol = [TC] - [HDL-cholesterol] - [TG/5]. Note: Nonfasting values differ from fasting values, but may still provide useful—though more limited—information. It may be inconvenient for the patient to return for a fasting sample. Costs may vary depending on which lipids (TC, HDL, LDL, VLDL, TG) are requested. At many institutions, a panel is available. Clinical decisions should be based on two lipid profiles, done 1 to 8 weeks apart, which have an LDL-cholesterol or TC difference of <30 mg/dL.
What other important risk factors for CHD should be assessed?	

NHLBI (2001 & 2004)	• Assessment of major risk factors* (exclusive of LDL-cholesterol) that modify LDL goals is recommended. Factors to assess include:
	  • Cigarette smoking
	  • Hypertension
	  • Low HDL-cholesterol (<40 mg/dL)**
	  • Family history of premature CHD
	  • Age (men ≥45 years, women ≥55years)
	
	  *Diabetes is regarded as a CHD risk equivalent.
	
	  **HDL cholesterol ≥60 mg/dL counts as a "negative" risk factor; its presence removes 1 risk factor from the total count
	
	• A 10-year risk assessment using Framingham scoring in persons identified to have multiple (2+) risk factors is recommended in order to identify individuals whose short-term (10-year) risk warrants consideration of intensive treatment.
	• In addition, assessment of life-habit risk factors and emerging risk factors is recommended. The former include obesity, physical inactivity, and atherogenic diet; the later consist of lipoprotein (a), homocysteine, prothrombotic and proinflammatory factors, impaired fasting glucose, and evidence of subclinical atherosclerotic disease.
	
	2004 Addendum
	
	• Lifestyle-related risk factors include obesity, physical inactivity, elevated triglycerides, low HDL-C, or metabolic syndrome.

USPSTF (2001)	• Treatment decisions should take into account overall risk of heart disease rather than lipid levels alone. Overall risk assessment should include the presence and severity of the following risk factors: age, gender, diabetes, elevated blood pressure, family history (in younger adults), and smoking. Tools that incorporate specific information on multiple risk factors provide more accurate estimation of cardiovascular risk than categorizations based on counting the numbers of risk factors.
UMHS (2003)	Major CHD Risk Factors other than LDL-cholesterol: • Cigarette smoking • Hypertension (blood pressure ≥140/90 mm Hg or on antihypertensive medication) • Low HDL-cholesterol (<40 mg/dL) * • Family history of premature CHD (CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years) • Age (men ≥45 years: women ≥55 years) Note: Diabetes is regarded as a CHD risk equivalent. *HDL cholesterol ≥60 mg/dL counts as a "negative" risk factor; its presence removes 1 risk factor from the total count.

VHA/DoD (2001)	• Proven, independent, clinical predictors of increased risk for ASCVD (in addition to elevated LDL-cholesterol) include:
	  • Age (males >45 years, females >55 years or menopause < age 40)
	  • Family history of premature coronary artery disease; definite myocardial infarction (MI) or sudden death before age 55 in father or other male first-degree relative, or before age 65 in mother or other female first-degree relative
	  • Current cigarette smoker
	  • Hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg confirmed on more than one occasion, or current therapy with antihypertensive medications)
	  • Diabetes mellitus (DM)
	  • HDL-cholesterol <40 mg/dL
	
	Quality of Evidence = I; Strength of Recommendation = A (Multiple Risk Factor Intervention Trial [MRFIT], 1982; Neaton & Wentworth, 1992; Castelli, 1984).

How should serum lipid concentrations be classified in terms of risk?	

NHLBI (2001 & 2004)	ATP III Classification of LDL, Total, and HDL-Cholesterol (mg/dL) • LDL-cholesterol — (primary target of therapy) <100 Optimal 100-129 Near Optimal/Above Optimal 130-159 Borderline High 160-189 High ≥190 Very high • Total cholesterol <200 Desirable 200-239 Borderline High ≥240 High • HDL-cholesterol <40 Low ≥60 High
USPSTF (2001)	• Not stated
UMHS (2003)	ATP III classification of LDL-cholesterol, Total, and HDL-cholesterol (mg/dL) • LDL-cholesterol <100 Optimal 100-129 Near or above optimal 130-159 Borderline high 160-189 High ≥190 Very high • Total cholesterol <200 Desirable 200-239 Borderline high ≥240 High • HDL-cholesterol <40 Low ≥60 Optimal
VHA/DoD (2001)	• TC<200 mg/dL or LDL-cholesterol <130 mg/dL AND HDL-cholesterol >35 mg/dL (in the absence of other risk factors) indicates a patient at average or below average risk for an atherosclerotic event in the next 5 years. • TC >200 mg/dL but fasting LDL-cholesterol <130 mg/dL AND HDL-cholesterol >40 mg/dL indicates a patient will be of average risk for lipid-related events over a one to two year period.
What is the significance of the lipid screening results for future	

management decisions?	

NHLBI (2001 & 2004)	• If an initial nonfasting test reveals a total cholesterol >200 mg/dL or an HDL <40mg/dL, a follow-up lipoprotein profile is needed for appropriate management based on LDL.
	• Any person with elevated LDL-cholesterol or other form of hyperlipidemia should undergo clinical or laboratory assessment to rule out secondary dyslipidemia before initiation of lipid-lowering therapy. Causes of secondary dyslipidemia include diabetes, hypothyroidism, obstructive liver disease, chronic renal failure, and certain drugs (e.g., progestins, anabolic steroids, corticosteroids).
	• Framingham projections of 10-year absolute CHD risk are used to identify certain patients with multiple (2+) risk factors for more intensive treatment.
	• Patients who are identified with multiple metabolic risk factors (metabolic syndrome) are candidates for intensified therapeutic lifestyle changes.
	• ATP III identifies three categories of risk that modify the goals and modalities of LDL-lowering therapy (see also relevant changes noted in the 2004 addendum presented below).
	  • CHD and CHD risk equivalents: LDL goal <100 mg/dL
	  • Multiple (2+) risk factors: LDL goal <130 mg/dL
	  • Zero to one risk factor: LDL goal <160 mg/dL
	• LDL goals in primary prevention depend on a person's absolute risk for CHD (i.e., the probability of having a CHD event in the short term or the long term)—the higher the risk, the lower the goal. Therapeutic lifestyle changes are the foundation of clinical primary prevention. Nonetheless, some persons at higher risk because of high or very high LDL cholesterol levels or because of multiple risk factors are candidates for LDL-lowering drugs. Recent primary prevention trials show that LDL-lowering drugs reduce risk for major coronary events and coronary death even in the short term (see also relevant changes noted in the 2004 addendum presented below).
	
	2004 Addendum
	
	The ATP III goals and cutpoints for therapeutic lifestyle changes and drug therapy in different risk categories, and proposed modifications in the treatment algorithm for LDL cholesterol based on evidence from recent clinical trials, are presented below. Essential modifications are highlighted in the footnotes and summary that follow.
	
	Risk Category: High risk: CHD[1] or CHD risk equivalents[2] (10-year risk >20%)
	
	• LDL-C Goal: [6]
	• Initiate TLC: >100 mg/dL[8]

- Consider Drug Therapy[9]: >100 mg/dL10 ([9]

Risk Category: Moderately high risk: 2+ risk factors[3] (10-year risk 10% to 20%)[4]

- LDL-C Goal: [7]
- Initiate TLC: >130 mg/dL[8]
- Consider Drug Therapy[9]: >130 mg/dL (100-129 mg/dL: consider drug options)[11]

Risk Category: Moderate risk: 2+ risk factors[3] (10-year risk <10%)[4]

- LDL-C Goal:
- Initiate TLC: >130 mg/dL
- Consider Drug Therapy[9]: >160 mg/dL

Risk Category: Lower risk: 0-1 risk factor[5]

- LDL-C Goal:
- Initiate TLC: >160 mg/dL
- Consider Drug Therapy9: >190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)

[1]Coronary heart disease (CHD) includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia.

[2]CHD risk equivalents include clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease [transient ischemic attacks or stroke of carotid origin or >50% obstruction of a carotid artery]), diabetes, and 2+ risk factors with 10-year risk for hard CHD >20%.

[3]Risk factors include cigarette smoking, hypertension (BP >140/90 mm Hg or on antihypertensive medication), low high-density lipoprotein (HDL) cholesterol (45 years; women >55 years).

[4]Electronic 10-year risk calculators are available at www.nhlbi.nih.gov/guidelines/cholesterol.

[5]Almost all people with zero or 1 risk factor have a 10-year risk

[6]Very high risk favors the optional LDL-C goal of

[7]Optional LDL-C goal

[8]Any person at high risk or moderately high risk who has lifestyle-related risk factors (e.g., obesity, physical inactivity, elevated triglyceride, low HDL-C, or metabolic syndrome) is a candidate for therapeutic lifestyle changes to modify these risk factors regardless of LDL-C level.

[9]When LDL-lowering drug therapy is employed, it is advised that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels.

[10]If baseline LDL-C is

[11]For moderately high-risk persons, when LDL-C level is 100 to 129 mg/dL, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level

Summary of Modifications

- Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. TLC has the potential to reduce cardiovascular risk through several mechanisms beyond LDL lowering.
- In high-risk persons, the recommended LDL-C goal is
    - An LDL-C goal of
    - If LDL-C is >100 mg/dL, an LDL-lowering drug is indicated simultaneously with lifestyle changes.
    - If baseline LDL-C is
    - If a high-risk person has high triglycerides or low HDL-C, consideration can be given to combining a fibrate or nicotinic acid with an LDL-lowering drug. When triglycerides are >200 mg/dL, non-HDL-C is a secondary target of therapy, with a goal 30 mg/dL higher than the identified LDL-C goal.
- For moderately high-risk persons (2+ risk factors and 10-year risk 10% to 20%), the recommended LDL-C goal is
- Any person at high risk or moderately high risk who has lifestyle-related risk factors (e.g., obesity, physical inactivity, elevated triglyceride, low HDL-C, or metabolic syndrome) is a candidate for TLC to modify these risk factors regardless of LDL-C level.
- When LDL-lowering drug therapy is employed in high-risk or moderately high-risk persons, it is advised that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels.
- For people in lower-risk categories, recent clinical trials do not modify the goals and cutpoints of therapy.

USPSTF (2001)	• In patients with elevated risk on screening results, lipoprotein analysis including fasting triglycerides may provide information that is useful in choosing optimal treatments. • Treatment decisions should take into account overall risk of heart disease rather than lipid levels alone. Tools that incorporate specific information on multiple risk factors provide more accurate estimation of cardiovascular risk than categorization based on counting the number of risk factors. • Although diet therapy is appropriate initial therapy for most patients, a minority achieve substantial reductions in lipid levels from diet alone; drugs are frequently needed to achieve therapeutic goals, especially for high-risk persons. Lipid-lowering treatments should be accompanied by interventions addressing all modifiable risk factors for heart disease, including smoking cessation, treatment of blood pressure, diabetes, and obesity, and promotion of a healthy diet and regular physical activity. Long-term adherence to therapies should be emphasized.

UMHS (2003)	• If initial testing reveals an HDL-cholesterol $\geq$40 mg/dL and either (a) TC $\leq$240 mg/dL or (b) TC $\leq$200 mg/dL with 2 or more CHD risks, the clinician should reinforce lifestyle education (smoking cessation, diet, exercise, weight loss) and repeat screening in 5 years.
	• If initial testing reveals an HDL-cholesterol $\leq$40 mg/dL or TC $\geq$240 mg/dL or TC >200 mg/dL with 2 or more CHD risks, the clinician should:
	  • Obtain a fasting lipid profile
	  • Consider and treat secondary causes (including, nephrotic syndrome, diabetes mellitus, obstructive liver disease, hypothyroidism, chronic renal failure, obesity, ethanol use, inactivity, and smoking)
	  • Recommend lifestyle modifications (smoking cessation, diet, exercise, weight loss, reduction of excessive alcohol). [Level of Evidence: A]
	• Patients with elevated LDL-cholesterol should have treatment tailored to CHD risks, with lower levels of LDL-cholesterol initiating treatment and lower LDL-cholesterol targets for those at increased risk. Coronary risk equivalents include established atherosclerotic disease, diabetes, and a (Framingham-based) Global Risk Score >2% annually.

VHA/DoD (2001)	Is Lipid Profile Abnormal? Patients with the following results of lipid measurements will require therapy for a lipid disorder: • LDL >130 mg/dL • HDL <40 mg/dL

	• TG >400 mg/dL Consider and Treat Secondary Causes of Elevated LDL-Cholesterol Hypothyroidism, chronic renal failure, and the nephrotic syndrome are well known to cause elevated LDL-cholesterol. Recognition of these conditions will focus attention on a potentially treatable underlying disorder. Cost-effective screening of the patient presenting with hypercholesterolemia might therefore include measurement of serum thyroid-stimulating hormone (TSH), BUN/creatinine, and a dipstick urinalysis, to exclude these relatively common conditions. Other causes of secondary dyslipidemia include diabetes mellitus, ethanol use, human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), obesity, smoking, obstructive liver disease, inactivity, and estrogen use. Quality of Evidence=III; Strength of Recommendation=A (Stone, 1997; NCEP III, 2001). Determine Goal of Therapy; Initiate/Modify Therapy to Achieve Goal Treatment should be based on LDL-cholesterol and CHD risk. CHD risk factors are age, family history, current smoker, hypertension, diabetes, and HDL-cholesterol <40 mg/dL. Patients with CHD or multiple risk factors require more aggressive treatment. Non-Pharmacologic Therapy Lifestyle change is indicated in all patients with 2 risk factors and LDL >130 mg/dL (>100 mg/dL for known CHD or diabetes). Strategies include diet, exercise, smoking cessation, cessation of excessive alcohol, and weight control. Pharmacologic Therapy Drug therapy is indicated in CHD/ASCVD patients and moderate-high risk primary prevention patients who remain above LDL thresholds with non-pharmacologic measures.
How frequently should patients be screened?	
NHLBI (2001 & 2004)	• Screening is recommended every 5 years unless more frequent testing is warranted. • Follow-up lipoprotein analysis should be carried out according to the following schedule: • In patients with 2+ risk factors whose LDL levels are observed at <130 mg/dL, lipoprotein analysis should be repeated $\leq$2 years;

	• In patients with 0-1 risk factors whose LDL levels are observed at 130-159 mg/dL, lipoprotein analysis should be repeated ≤2 years, • In patients with 0-1 risk factors whose LDL levels are observed at <130 mg/dL, lipoprotein analysis should be repeated ≤5 years.
USPSTF (2001)	• The optimal interval for screening is uncertain. Based on other guidelines and expert opinion, reasonable options include: every 5 years, shorter intervals for persons who have lipid levels close to those warranting therapy, and longer intervals for low-risk persons who have had low or repeatedly normal lipid levels.
UMHS (2003)	• Patients with normal screening lipids are generally rechecked at 5-year intervals, as lipids may gradually worsen over time and they may develop secondary causes later in life [Level of Evidence: D]. Patients with borderline values, not requiring therapy, may be rechecked at 1-2 year intervals. Patients with the metabolic syndrome are at particular risk and merit both more frequent testing and lower thresholds for intervention.

VHA/DoD (2001)	• Repeat dyslipidemia evaluation in 1 to 5 years if the initial dyslipidemia screening reveals TC <200 mg/dL or LDL cholesterol <130 mg/dL AND HDL-cholesterol >35 mg/dL.
	  • The patient—in the absence of other risk factors—will be of average or below average risk for atherosclerotic events over a five-year period. Because total and LDL cholesterol tend to increase with advancing age, patients at initially average risk for ASCVD events may over time become patients at above-average risk or may develop concurrent health conditions (nephrotic syndrome, hypothyroidism, diabetes mellitus) that can declare as dyslipidemia.
	  • Reassessment of serum cholesterol and HDL five years after an initially favorable dyslipidemia screening permits timely identification and treatment of such individuals.
	
	Quality of Evidence=III; Strength of Recommendation=A (NCEP III, 2001; Lovastatin Study Groups, 1993; Jones et al., 1991).
	• Repeat dyslipidemia evaluation in 1 to 2 years if the initial dyslipidemia screening reveals TC >200 mg/dL but fasting LDL-cholesterol <130 mg/dL AND HDL cholesterol >40 mg/dL. The patient will be of average risk for lipid-related events over a

	one to two year period.

TABLE 3: BENEFITS/HARMS OF LIPID SCREENING	
Benefits of Lipid Screening	
NHLBI (2001 & 2004)	• By adopting the clinical high-risk CHD prevention strategy, individuals at significantly increased risk are identified and treated, thus reducing the individual's risk for CHD and reducing the overall burden of CHD. The clinical high-risk strategy and the population strategy, which seeks to lower average blood cholesterol levels in the whole population by promoting changes in dietary patterns and physical activity levels, are complementary. Both strategies are incorporated into the National Cholesterol Education Program and together reduce the societal burden of CHD. 2004 Addendum • Since the publication of ATP III, 5 major clinical trials of statin therapy have confirmed the benefit of cholesterol-lowering therapy in high-risk patients and support the ATP III treatment goal of low-density lipoprotein cholesterol (LDL-C)
USPSTF (2001)	• The clearest benefit of lipid screening is identifying individuals whose near-term risk of coronary heart disease is sufficiently high to justify drug therapy or other intensive lifestyle interventions to lower cholesterol. Screening men over age 35 and women over age 45 will identify nearly all individuals whose risk of coronary heart disease is as high as that of the subjects in the existing primary prevention trials. In a population with a 1% risk of coronary heart disease per year, drug treatment of 67 persons for 5 years is required to prevent 1 coronary heart disease event. Most younger persons have a substantially lower risk, unless they have other important risk factors for coronary heart disease or familial hyperlipidemia.
UMHS (2003)	• Screening will help identify patients who may benefit from lipid lowering therapy. LDL-cholesterol-based drug therapy for primary prevention has been shown to reduce future cardiovascular events. In high-risk populations, this therapy has also been shown to reduce mortality.

VHA/DoD (2001)	• Lipid-related risk factors for ASCVD include high levels of total cholesterol or low-density lipoprotein cholesterol (LDL-cholesterol) and low levels of high-density lipoprotein cholesterol (HDL-cholesterol). Other risk factors include age, male sex, high blood pressure, tobacco use, diabetes mellitus, and family history of premature coronary heart disease. Targeted screening to identify these risk factors will allow for lipid-related interventions to reduce the risk of ASVCD.
Harms of Screening	
NHLBI (2001 & 2004)	• Not stated
USPSTF (2001)	• Studies of adverse effects of screening are limited but have not found adverse psychological effects (i.e. labeling) in patients identified with abnormal lipids. • Screening could subject some low-risk persons to the inconvenience and expense of treatments that may offer only minimal benefits.
UMHS (2003)	• Not stated
VHA/DoD (2001)	• Not stated

TABLE 4: EVIDENCE AND RECOMMENDATION RATING SCHEMES	
NHLBI (2001 & 2004)	Type of Evidence: A. Major randomized controlled trials B. Smaller randomized controlled trials and meta-analyses of other clinical trials C. Observational and metabolic studies D. Clinical experience Strength of Evidence: 1. Very strong evidence 2. Moderately strong evidence

	3. Strong trend
USPSTF (2001)	The U.S. Preventive Services Task Force (USPSTF) grades the quality of the overall evidence on a 3-point scale (good, fair, or poor). Good: Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes. Fair: Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of evidence on health outcomes. Poor: Evidence is insufficient to assess the effects on health outcomes because of limited number of power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes. The U.S. Preventive Services Task Force (USPSTF) grades its recommendations according to one of five classifications (A, B, C, D, or I), reflecting the strength of evidence and magnitude of net benefit (benefits minus harms). A: The U.S. Preventive Services Task Force (USPSTF) strongly recommends that clinicians routinely provide [the service] to eligible patients. (The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.) B: The U.S. Preventive Services Task Force (USPSTF) recommends that clinicians routinely provide [the service] to eligible patients. (The USPSTF found at least fair evidence that [the service] improves health outcomes and concludes that benefits outweigh harms.) C: The U.S. Preventive Services Task Force (USPSTF) makes no recommendation for or against routine provision of [the service]. (The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.) D: The U.S. Preventive Services Task Force (USPSTF) recommends against routinely providing [the service] to asymptomatic patients. (The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.)

	I: The U.S. Preventive Services Task Force (USPSTF) concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. (Evidence that [the service] is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.)
UMHS (2003)	Levels of evidence reflect the best available literature in support of an intervention or test: A. Randomized controlled trials B. Controlled trials, no randomization C. Observational trials D. Opinion of expert panel
VHA/DoD (2001)	RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE Quality of Evidence Grading I: Evidence is obtained from at least one properly randomized clinical trial (RCT) II-1: Evidence is obtained from well-designed controlled trials without randomization. II-2: Evidence is obtained from well-designed cohort or case-control analytical studies, preferably from more than one center or research group. II-3: Evidence is obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940's) could also be regarded as this type of evidence. III: Opinions of respected authorities are based on clinical experience, descriptive studies and case reports, or reports of expert committees. RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS The rating scheme used for this guideline is based upon a system used by the U.S. Preventive Services Task Force (USPSTF, 1996). The scheme is as follows: Strength of Recommendation Grading:

A. There is good evidence to support the recommendation that the condition be specifically considered.
B. There is fair evidence to support the recommendation that the condition be specifically considered.
C. There is insufficient evidence to recommend for or against the inclusion of the condition, but recommendations may be made on other grounds.
D. There is fair evidence to support the recommendation that the condition be excluded from consideration.
E. There is good evidence to support the recommendation that the condition be excluded from consideration.

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GUIDELINE CONTENT COMPARISON

The National Heart, Lung and Blood Institute (NHLBI), the United States Preventive Services Task Force (USPSTF), the University of Michigan Health Systems (UMHS), and the Veterans Health Administration, Department of Defense (VHA/DoD) present recommendations for screening for high cholesterol among adults for primary prevention of CHD and ASCVD. The NHLBI, UMHS, and VHA/DoD guidelines also contain recommendations for clinical management of high blood cholesterol and secondary prevention in patients with existing CHD or ASCVD; these topics will be included in a separate synthesis.

All of the guidelines in the current comparison describe the clinical evidence and give explicit reasoning for their recommendations. UMHS presents its guideline in the form of an algorithm, accompanied by tables and a discussion of the clinical evidence supporting the recommendations. VHA/DoD also presents its guideline in algorithmic form, with accompanying annotations and discussions that expand on the recommendations and statements found in each box of the algorithm. These annotations include an evidence grading for each recommendation, followed by a reference list that includes all of the sources used in the development of the annotations. The NHLBI guideline and addendum contain both detailed discussions of the clinical evidence and summary algorithms. NHLBI provides graded evidence statements in the original guideline document. All of the guidelines grade the evidence supporting their recommendations using a pre-specified rating scheme.

Areas of Agreement

Which Screening Tests Should be Used?

There is agreement among all of the guidelines that initial screening should include either fasting or non-fasting tests for total cholesterol (TC) and high-density lipoprotein (HDL) cholesterol. NHLBI specifically recommends the fasting lipid profile, which includes measurement of TC, triglycerides, HDL-cholesterol, and LDL-cholesterol (direct or calculated) in preference to the nonfasting tests. The rationale for this preference is discussed further below under areas of disagreement.

Serum Lipid Concentrations and Risk

The classification scheme of total, LDL and HDL-cholesterol levels used by UMHS and VHA/DoD is derived from the NHLBI ATP II/ATP III guidelines (USPSTF does not address this topic in its guideline). A total cholesterol concentration <200 mg/dL represents a "normal" or "desirable" blood cholesterol level; a concentration between 200 and 239 mg/dL is "borderline," and $\geq$240 mg/dL is "high". Critical values for LDL-cholesterol are 130-159 mg/dL (borderline) and $\geq$160 mg/dL (high-risk). HDL-cholesterol levels are considered optimal at $\geq$60 mg/dL, while HDL-cholesterol levels below 35-40 mg/dL will place patients at high

risk for CHD. ATP III specifically states that "low" HDL-cholesterol should be defined as <40 mg/dL because this is a better measure of depressed HDL than <35 mg/dL.

Significance of Lipid Screening Results and Future Management Decisions

There is also general agreement among all guideline groups that any further management decisions should be based on CHD risk assessment as well as results of lipid screening. The core set of risk factors (excluding LDL-cholesterol) for CHD includes advanced age, hypertension, obesity, family history of CHD, cigarette smoking, diabetes mellitus type II, and low HDL-cholesterol levels. NHLBI and UMHS go a step beyond simple counting of risk factors by recommending use of Framingham projections of 10-year absolute CHD risk to identify certain patients with $\geq$2 risk factors for more intensive treatment. All of the guidelines also recommend that secondary causes of dyslipidemia, such as diabetes mellitus, obstructive liver disease, hypothyroidism, use of certain drugs, and ethanol use, need to be investigated and addressed before initiation of lipid-lowering therapy.

For primary prevention of CHD, lifestyle changes (e.g., diet, exercise, smoking cessation) are recommended by UMHS and VHA/DoD, when LDL-cholesterol is above 130 mg/dL in patients with 2 or more CHD risk factors. Similarly, drug therapy is recommended by these two groups when LDL-cholesterol is above 160 mg/dL in patients with 2 or more CHD risk factors, and above 190 mg/dL in patients with less than 2 CHD risk factors. With the 2004 addendum, NHLBI modified the recommendations for initiation of therapeutic lifestyle changes (TLC) and drug therapy. This is discussed further under areas of disagreement. The USPSTF does not address initiation of therapy in their guideline.

Screening Frequency

The guidelines advocate repeated screening at least once every five years in persons with no or low risk factors for CHD. Depending on the results of the initial lipid screen, testing may occur more frequently. In addition, testing should occur more often in persons whose TC approaches a threshold for initiating treatment.

HDL-cholesterol

While all of the groups included in this synthesis recognize that low HDL-cholesterol is a strong independent predictor of CHD, none of them specifically recommend treating low HDL-cholesterol nor do they specify a goal for raising HDL. NHLBI reports there is insufficient evidence to specify such a goal and also notes the lack of available drugs for treating low HDL-cholesterol. NHLBI instead focuses on LDL cholesterol as the primary target of therapy.

Areas of Difference

Who Should be Screened?

Who should be screened for dyslipidemia is one of the major areas of disagreement among the four guideline groups. NHLBI recommends lipid screening for all individuals starting at 20 years of age, based on evidence that

CHD disease develops in a continuous fashion, often beginning in the early twenties. They also argue that early awareness may encourage healthy behaviors. Furthermore, waiting until age 35 in men and age 45 in women may result in missed opportunities for early intervention. The other three guideline groups (USPSTF, UMHS, and VHA/DoD) do not recommend screening before age 35 for men and before age 45 for women unless the individuals have multiple risk factors for CHD or a history suggestive of familial hyperlipidemia. These guidelines present evidence that the short-term risk for developing CHD is low in these groups, even among those with an elevated cholesterol level, and the potential benefits of cholesterol reduction are small and thus not cost-effective. None of the guidelines identified randomized clinical trials that provided direct evidence on the effects of cholesterol reduction in these age groups.

NHLBI and USPSTF do not indicate an upper age limit for lipid screening and maintain that age alone should not be reason to withhold the benefits of cholesterol lowering. UMHS and VHA/DoD, on the other hand, suggest upper age limits of 75 years for testing, based on a lack of benefit of treatment in this age group.

Which Screening Tests Should be Used?

As mentioned above, NHLBI recommends use of a fasting TC, triglyceride, and HDL-cholesterol profile for initial screening in preference to a nonfasting test for TC and HDL-cholesterol only. Their rationale is that LDL-cholesterol levels cannot be accurately calculated from nonfasting profiles; therefore, fasting profiles are essential if management is to be based on LDL-cholesterol levels. Moreover, TC levels may overestimate the risk of CHD in patients with high TC values due to high HDL-cholesterol. Finally, measurement of triglycerides is viewed as important in light of two meta-analyses (Austin MA, Hokanson JE, Edwards KL. Hypertriglyceridemia as a cardiovascular risk factor. Am J Cardiol 1998;81:7B-12B.; and, Assmann G, Schulte H, Funke H, von Eckardstein A. The emergence of triglycerides as a significant independent risk factor in coronary artery disease. Eur Heart J 1998a;19(suppl M):M8-M14.) of prospective studies, which indicate that elevated triglycerides are an independent risk factor for CHD. UMHS and VHA/DoD, while acknowledging the superiority of the fasting profile, recommend its use as a follow-up test when results of initial nonfasting profiles are abnormal. USPSTF states that the evidence for or against triglyceride measurement as part of routine screening is conflicting. USPSTF further argues that even if elevated triglycerides are independently associated with increased CHD risk, it is unclear that treating individuals with isolated hypertriglyceridemia will reduce future CHD events. The added cost and inconvenience to patients are other reasons that are given to justify using nonfasting tests in the initial screening.

Significance of Lipid Screening Results and Future Management Decisions

LDL cholesterol

Although the other guidelines included in this Synthesis drew heavily from the ATP II and ATP III reports, recent statin trials have provided new information on benefits of LDL-lowering therapy applied to persons in categories in which ATP III could not make definitive recommendations about drug therapy. To this point, only the 2004 NHLBI guideline addendum has issued modified LDL-C goals and

cutpoints for initiation of therapeutic lifestyle changes and drug therapy. These changes include the expansion of risk categories from 3 to 4 defined as:

- High Risk: CHD or CHD risk equivalents (10-year risk >20%)
- Moderately High Risk: 2+ risk factors (10-year risk 10% to 20%)
- Moderate Risk: 2+ risk factors (10-year risk <10%)
- Lower Risk: 0-1 risk factor

TLC is recommended in high-risk patients whenever the LDL-C level is >100 mg/dL. Furthermore, any person at high risk who has lifestyle-related risk factors (e.g., obesity, physical inactivity, elevated triglycerides, low HDL-C, or metabolic syndrome) is a candidate for TLC to modify these risk factors regardless of LDL-C level. As before, whenever the baseline LDL-C concentration is >130 mg/dL, simultaneous initiation of an LDL-lowering drug and dietary therapy is recommended. If LDL-C is 100 to 129 mg/dL, the same now holds. If baseline LDL-C is

For patients at moderately high risk (10-year risk 10% to 20%), the LDL-C goal remains 130 mg/dL. Again, any person at moderately high risk who has lifestyle-related risk factors (e.g., obesity, physical inactivity, elevated triglycerides, low HDL-C, or metabolic syndrome) is a candidate for TLC to modify these risk factors regardless of LDL-C level. If the LDL-C concentration is >130 mg/dL after TLC, consideration should be given to initiating an LDL-lowering drug, to achieve and sustain the LDL-C goal of

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This Synthesis was prepared by NGC on July 28, 2000. It was reviewed by the guideline developers as of October 10, 2000. It has been modified a number of times. The most recent version removes the AACE guidelines, which have been archived.

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